APPROVAL SHEET

Title of Thesis: "Atypical Depression, Body Mass, and Left Ventricular Mass: Analysis of Data from CARDIA"

Name of Candidate: Sari D. Schwartz
Master of Science Degree
2005

Thesis and Abstract Approved:

_____ _____
David S. Krantz, Ph.D. Date
Thesis Advisor

_____ _____
Willem J. Kop, Ph.D. Date
Committee Member

_____ _____
Martha M. Faraday, Ph.D. Date
Committee Member

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
2005		**00-00-2005 to 00-00-2005**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Atypical Depression, Body Mass, and Left Ventricular Mass: Analysis of Data from Cardia	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Uniformed Services University of the Health Sciences,F. Edward Hebert School of Medicine,4301 Jones Bridge Road,Bethesda,MD,20814-4799**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES
The original document contains color images.

14. ABSTRACT
see report

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**		**71**	

COPYRIGHT STATEMENT

The author hereby certifies that the use of any copyrighted material in this thesis manuscript entitled:

"Atypical Depression, Body Mass, and Left Ventricular Mass: Analysis of Data from CARDIA"

beyond brief excerpts is with permission of the copyright owner, and will save and hold harmless the Uniformed Services University of the Health Sciences from any damage which may arise from such copyright violations.

Sari D. Schwartz
Department of Medical and Clinical Psychology
Uniformed Services University of the Health Sciences

ABSTRACT

Title of Thesis: Atypical Depression, Body Mass, and Left Ventricular Mass: Analysis of Data from CARDIA

Sari D. Schwartz, Master of Science, 2005

Thesis directed by: David S. Krantz, Ph.D.

Professor & Chair

Department of Medical and Clinical Psychology

This study investigated possible relationships among subtypes of depression (typical vs. atypical), body mass, and left ventricular mass (LVM). Data from the CARDIA study (years 5 and 10) were used to investigate the model. Depression subtype was determined from CES-D scores at year 5 identifying atypical depression (AD) specifier symptoms. Body mass index (BMI) was calculated at years 5 and 10 (kg/m2). M-mode echocardiography ascertained LVM at years 5 and 10. BMI increases were significantly associated with LVM increases ($p<0.001$). There was a race-by-sex-by-depression group interaction ($p=0.016$), such that depression was associated with year 10 LVM in white males only, but AD did not fully explain the relationship. Mediational analyses indicated that in white males, BMI mediated all depression subtype associations with LVM except the AD vs. typical depression comparison. These results suggest the potential importance of depression subtypes in CVD risk assessment. The model and three-way interaction should be investigated further.

ATYPICAL DEPRESSION, BODY MASS, AND LEFT VENTRICULAR MASS: ANALYSIS OF DATA FROM CARDIA

by

Sari D. Schwartz

Thesis submitted to the Faculty of the

Medical and Clinical Psychology Graduate Program

Uniformed Services University of the Health Sciences

in partial fulfillment of the requirements for the degree of

Master of Science, 2005

ACKNOWLEDGMENTS

I would like to extend my sincere appreciation to Dr. David Krantz, who has encouraged and supported my research and academic endeavors. His research achievements and guidance as a mentor have provided me with an invaluable role model for my own career. Also, I would like to thank my committee members, Dr. Wijo Kop and Dr. Martha Faraday, who have been instrumental in completion of this project. Finally, I am honored to have shared this experience with all of the graduate students in the Department of Medical and Clinical Psychology. Their support, feedback, and intellectual exchange shape the student and person I strive to become.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Background

Cardiovascular disease (CVD) is the leading cause of death for people in industrialized countries. In addition, the lifetime prevalence rate of major depression in the United States is reported to be 13% in the population (Kessler et al., 1994). Not only are depression and cardiovascular disease highly prevalent illnesses, they are also interrelated. Although depression is commonly thought of as a risk factor for adverse outcomes after a cardiac event has occurred (Carney et al., 1988; Frasure-Smith et al., 1993 and 1995), there is evidence for depression as a risk factor for developing cardiovascular disease (Aromaa et al., 1994; Pratt et al., 1996). Therefore, depression has been implicated as an independent risk factor for the pathophysiologic progression of CVD, rather than as only a secondary emotional response to the illness (Musselman et al., 1998; Wulsin & Singal, 2003). The purpose of the present study was to explore the link between depression and risk of cardiovascular disease using left ventricular mass, a measure of heart size, as an index of cardiovascular risk. This thesis will begin with an introduction to depression, subtypes of depression, the relationship of depression to CVD, and factors associated with left ventricular mass.

Depression

Definition and Measurement

The DSM-IV (APA, 1994) defines depression as a two-week or longer period during which an individual experiences depressed mood or loss of interest that significantly affects functioning. A total of five of the nine symptoms are required for a

diagnosis of Major Depressive Disorder, one of which must be depressed mood or loss of interest. The other symptoms include: insomnia or hypersomnia, significant increase or decrease in appetite or weight, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate guilt, decrease in concentration or indecisiveness, and suicidal ideation or behavior.

There are many ways to measure and conceptualize depression. Some measurements focus on a binary clinical diagnosis or illness severity, whereas others measure continuous levels of depression symptomatology for the purpose of studying depression as it relates to other variables. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1996) is used for the purpose of clinical assessment. This measure produces diagnostic results regarding whether or not a person experiences clinical depression. However, it may be informative for certain research questions to obtain information about the level of depression and symptoms not only a dichotomous diagnostic decision. The Center for Epidemiologic Studies Depression Scale (CES-D) was designed for use in epidemiological studies to measure current levels of depressive symptoms in the general population (Radloff, 1977). Because the CES-D was developed for general population surveys, it is a short, structured, self-report measure that is usable by lay interviewers and respondents (Radloff, 1977). In addition, when conducting epidemiological studies it is helpful to utilize a measure that is well suited for identifying depression in the general population requiring less stringent diagnostic criteria. It is possible that a larger group suffering from depression in a population will be identified from measures that have lower thresholds than a clinical instrument.

Depressive syndromes that do not fulfill diagnostic criteria for specific depressive disorders are identified as "subclinical" depressive syndromes (Schneider, 2000). There is evidence that even subclinical depression poses a risk for adverse health outcomes. One such study examined the mortality risk after acute myocardial infarction from symptoms of depression that did not meet the clinically significant threshold (Bush et al., 2001). Four-month mortality among all patients with BDI $\geq$ 10 was 2.6 times greater as compared with patients with BDI scores < 10 ($p=0.06$). As expected, participants with the most severe depressive symptoms experienced the highest mortality rates. However, higher mortality was also observed at very low levels of depressive symptoms (BDI scores 4 to 9) that are not usually considered clinically significant and below the level usually considered predictive of increased post-AMI mortality (Bush et al., 2001). This study illustrates that measures such as the CES-D and the Beck Depression Inventory provide valuable information regarding depressive symptoms as a continuous variable.

Depression Subtypes

In addition to the main diagnosis of depression, the pattern of an individual's depressive symptoms may meet criteria for an atypical features specifier. Evidence has accumulated that suggests that atypical depression is a biologically distinct subtype of depression (Quitkin, 2002). Genetic epidemiologic studies indicate that depression with atypical features is genetically distinct from typical depression presentations (Kendler et al., 1996; Quitkin, 2002). In addition, researchers have shown a preferential response of the atypical subtype to monoamine oxidase inhibitors as compared with tricyclic antidepressants (Quitkin, 2002). In addition to mood reactivity (the ability for mood to

brighten in response to positive experiences), the atypical depression subtype requires two or more of the following symptoms: overeating (hyperphagia), oversleeping (hypersomnia), "leaden paralysis," and interpersonal rejection sensitivity. Research aimed at testing the DSM-IV criteria for the atypical specifier for depression found support for the current DSM-IV definition (Benazzi, 2003). However, Benazzi's work (2002) has also brought into question the necessity for the mood reactivity component of the atypical depression specifier in the interest of simplifying its definition and assessment. Conversely, typical depression is used to classify the depressive disorder of an individual experiencing such symptoms as reduced appetite, insomnia, and psychomotor agitation.

Although the name "atypical depression" implies that this symptom profile is less prevalent than typical depression, there is evidence to suggest that the prevalence of atypical depression is common, with approximately 15-40% of depressed individuals meeting criteria for atypical depression (Benazzi, 1999; Posternak & Zimmerman, 2002; Quitkin, 2002). Increased clinical severity, greater impairment, and increased service use have been associated with atypical depression as compared to typical depression (Angst et al., 2002).

Depression Associations with Cardiovascular Disease

Although there is evidence that psychosocial variables are related to prognosis in patients with established coronary disease, recent literature reviews have concluded that the cumulative evidence is greatest for depression (Frasure-Smith & Lesperance, 2003). Major depressive disorder (MDD) is experienced in approximately 15% to 20% of

patients with acute myocardial infarction (AMI; Frasure-Smith et al., 1993; Bush et al., 2001). Frasure-Smith and colleagues (1993; 1995) conducted a series of studies assessing the mortality risk associated with depression in cardiac patients. The authors utilized both the National Institute of Mental Health Diagnostic Interview Schedule (DIS) and Beck Depression Inventory (BDI) to assess depressive symptoms in patients approximately one week post-MI. Participants then were recontacted at 6 months and 18 months after hospital discharge to determine survival status. At the six month follow-up the mortality hazard ratio for depression (measured by DIS) was 3.44 (CI= 2.25 to 4.63) after adjusting for significant independent predictors of mortality and the baseline differences between depressed and non-depressed patients (i.e. - presence of close friends and gender). After 18 months of follow-up, analyses indicated that depression measured by both the DIS (OR=3.64, CI=1.32 to 10.05) and BDI (OR=7.82, CI=2.42 to 25.26) was still significantly related to increased cardiac mortality. These data demonstrate that the presence of MDD in the first few weeks after an MI increases the risk of mortality in cardiac patients and that there is a long term increase in risk of mortality associated with depression (Frasure-Smith et al., 1993; Frasure-Smith et al., 1995).

The literature associating depression with CVD also has shown that in otherwise healthy individuals, depression represents an independent risk for cardiovascular events and mortality. Prospective data from the Baltimore cohort of the Epidemiologic Catchment Area Study were used to determine the relationship between history of a major depressive episode and MI (Pratt et al., 1996). Results indicated that history of a major depressive episode significantly increased the risk of MI by 4.5, independent of other coronary disease risk factors. Ferketich et al. (2000) found that depression was

associated with an increased risk of coronary heart disease (CHD) incidence in men and women, increased risk of CHD mortality in men, but no effect on CHD mortality in women. The results from this longitudinal study provide supportive evidence of depression as an antecedent to CVD. In addition, a systematic review by Wulsin & Singal (2003) examined whether depression in the absence of comorbid CVD was predictive of future cardiovascular morbidity or mortality. The results of this quantitative review of ten studies suggest that depressive symptoms present a significant independent risk for the onset of coronary disease (RR=1.64, CI=1.41 to 1.90).

Mechanisms of Depression and Cardiovascular Disease Association

Musselman et al. (1998) describe the possible explanations for the relationship between depression in CV patients and poor outcome and prognosis. Biological pathways associating depression with CVD include hyperactive hypothalamic-pituitary-adrenocortical (HPA) axis (Nemeroff et al., 1984; Raadsheer et al., 1994), sympathoadrenal system dysregulation (Lechin et al., 1995), diminished heart rate variability (Dalack & Roose, 1990; Miyawaki & Salzman, 1991), and alterations in platelet receptors and/or reactivity (Markovitz & Matthews, 1991). Hyperactivity of the HPA axis in depressed individuals leads to overproduction and dysregulation of corticosteroids. Musselman et al. (1998) review evidence indicating that corticosteroids can induce hypertriglyceridemia, hypercholesterolemia, hypertension, injury of vascular endothelial cells, and coronary atherosclerosis (Troxler et al., 1977). Sympathoadrenal system dysregulation in depressed individuals is reflected by higher heart rate levels and greater plasma concentrations of norepinephrine and serotonin at rest (Lechin et al.,

1995). This sympathoadrenal hyperactivity may contribute to the development of CVD through the effects of catecholamines on cardiac function, blood vessels, and platelets (Musselman et al., 1998). It has been observed that compared to non-depressed individuals, depressed patients have reduced heart rate variability (HRV; Dalack & Roose, 1990; Miyawaki & Salzman, 1991). Reduction in HRV is purportedly associated with decreased parasympathetic tone, which could result in ventricular arrhythmias and/or cardiovascular mortality (Musselman et al., 1998). Platelet activation has been proposed as a mechanism through which depression in healthy young adults may act as a risk factor for CVD (Musselman et al., 1998). Musselman et al. (1996) found that depressed patients exhibited enhanced baseline platelet activation and responsiveness. It also has been found that platelet activation can lead to the development of atherosclerosis, thrombosis, and vasoconstriction (Musselman et al., 1998).

However, other more psychologically focused concepts are also important in the association between depression and CVD. For example, depressed individuals have problems with concentration and problem-solving and depression can adversely affect rehabilitation (Stern et al., 1977; Mayou et al., 1978) and medical regimen compliance (Blumenthal et al., 1982; Carney et al., 1995). There are also several established behavioral risk factors for CVD that have been found more frequently among depressed individuals including smoking, increased weight, and decreased physical activity. There is a link between depression and smoking, although the direction of this association is not clear (Steuber & Danner, 2005). The stimulant properties of nicotine have been proposed as appealing for depressed individuals as a manner of self-medication (Fergusson, Goodwin, & Horwood, 2003) whereas other researchers have found that smoking was a

strong predictor of developing depression (Wu & Anthony, 1999; Goodman & Capitman, 2000). In either instance, the relationship of depression with smoking tobacco provides a behavioral mechanism for CVD risk. A similar dichotomy exists regarding the direction of association between depression and obesity as well as depression and physical activity. Baseline obesity has been found to be predictive of increased depression risk (Roberts et al., 2002), while other research shows that baseline depression predicts greater BMI (Pine et al., 2001) and obesity at follow-up (Goodman & Whitaker, 2002). The physical activity literature has shown that those who reported low levels of physical activity were at greater risk for depression at follow-up than those who reported high levels of physical activity (Camacho et al., 1991). In addition, patients with more severe depression were found to have lower activity levels than less severely depressed patients and non-depressed medical controls (Iverson, 2004). Regardless of the direction, the relationship of depression with smoking tobacco, obesity, and reduced physical activity provides behavioral mechanisms for CVD risk.

Left Ventricular Mass

Definition and Factors Affecting Left Ventricular Mass

Left ventricular mass (LVM) refers to the physical size of the left ventricle. Over time, sustained elevations in blood pressure or left ventricular volume loads may lead to an increase in LVM, known as left ventricular hypertrophy. This enlargement of the left ventricle of the heart contributes to cardiovascular morbidity and mortality (Vakili et al., 2001; Taylor et al., 2003) and is predictive of poor prognosis independent of blood

pressure (Sharp & Mayet, 2002; Dei Cas et al., 2003). The potential etiologies leading to increases in LVM are hypertension, valvular disease, congenital heart disease, acromegaly (giantism), chronic renal failure, and Thalassemia (Cooley's Anemia). Hypertension is the most common factor leading to an increase in LVM because the heart and, in particular, the left ventricle have to increase workload to accommodate the increase in blood pressure. There are several hypotheses that attempt to explain the etiology of hypertension. The salt hypothesis states that cultures/countries that ingest a diet high in sodium have a higher prevalence of hypertension and related health problems because increased sodium levels are associated with elevated blood pressure (Saltos & Bowman, 1998). In population, animal, and twin studies, genetics have been shown to be important in the development of hypertension (Mullins et al., 1996; Mein et al., 2004; Sun & Zhang, 2005). The last major hypothesis for the development of hypertension is that there is an imbalance of vasodilators and vasoconstrictors causing an increase in blood pressure to maintain steady blood flow (Luscher, 1990; Brook & Julius, 2000; Schiffrin, 2001).

Blood Pressure and Weight

In addition to the mechanisms explaining left ventricular hypertrophy (LVH), a number of risk factors have been found to be related to LVM including blood pressure (BP; Gardin et al., 1995), age, sex, ethnicity, anthropometric characteristics, and alcohol and sodium consumption (Taylor et al., 2003). In addition to blood pressure, longitudinal research conducted by Urbina et al. (1995) has shown that excess weight might lead to the development of LVM beyond that expected for normal growth, which may

subsequently lead to LVH. Schirmer et al. (1999) graphed age-adjusted sex-specific prevalences of left ventricular hypertrophy against quintiles of body mass index (BMI) and systolic blood pressure (SBP) in individuals without a history of cardiovascular disease (See Figure 1). The authors concluded that BMI is the critical factor in LVH risk as compared to SBP.

Sex and Left Ventricular Mass

Research conducted by Gardin and colleagues (1987) report a relationship between sex and LVM such that females have a slightly smaller LVM than males for any given age and body surface area. Left ventricular mass, measured with M-mode echocardiography, also varies linearly with body surface area and increases as a function of age (Gardin et al., 1987). The findings of another study investigating factors associated with LVM in 111 healthy adults also suggested that LVM, as assessed by two-dimensional-guided M-mode echocardiography, is affected not only by sex and body size but also by age, but only in women (Shub et al., 1994).

Psychological Variables Related to Left Ventricular Mass

Evidence suggests an association between several psychosocial variables and LVM. Left ventricular mass index has been associated with high levels of job strain after controlling for age, race, body-mass index, type A behavior, alcohol intake, smoking, work site, 24-hour urine sodium excretion, education, and physical demand level of the job in male subjects aged 30 to 40 years (Schnall et al., 1990). The authors conclude that job strain may be a risk factor for structural changes of the heart in working men. There

are inconsistent findings in the literature regarding the relationship between hemodynamic reactivity to challenging, aversive, or engaging stimuli and LVM. A review by Taylor et al. (2003) found a modestly consistent relationship between hemodynamic reactivity and LVM with 43% of studies showing a relationship between SBP and LVM and 14% of studies showing a relationship between DBP and LVM. Research conducted on panic disorder patients found subclinical increases in LVM in the panic patients as compared to the normal controls, concluding that panic disorder might be associated with subclinical myocardial changes (Kahn et al., 1990). Gump et al. (1999) examined the relationship between socioeconomic status, hostility, cardiovascular reactivity, and LVM (adjusted for body surface area) in children. The authors found that for African Americans lower SES leads to higher hostility that in turn leads to higher cardiovascular reactivity and increased LVM. For Caucasians however, the variable of hostility was not significant in the model leaving a relationship between SES and cardiovascular reactivity followed by increased LVM. Another investigation of the relationship between psychosocial variables (depression, anxiety, hostility, anger suppression, and education) and LVM in young adults found that there was only an association between education and LVM across all participants and an association between depression and LVM in Caucasian women ($\beta=0.09\pm0.03$, $p=0.006$; Markowitz et al., 1996). This investigation by Markowitz and colleagues (1996) used the same data set as the present study (CARDIA) and is unique in its analysis of depression and left ventricular mass. There is a shortage of research, and in particular conclusive research, into the connections between LVM and psychological variables, which may represent an as yet untapped potential for behavioral and psychological mechanisms of CVD risk.

A symptom that is often experienced with depression is hyperphagia, or overeating. In particular, individuals with atypical depression, a subtype of major depression, demonstrate this feature of increased appetite and weight gain (Posternak & Zimmerman, 2001). Body mass index and change in body mass index predict LVM and LVH (Gardin et al., 2002; Dekkers et al., 2002). Therefore, an association may exist between depression and LVM through excess body weight and weight gain, frequently experienced by individuals with atypical depression. It is proposed that in previous studies the CVD risk associated with depression may have been attributable to the atypical subtypes in the research groups of depressed individuals.

CARDIA Study

The National Heart, Lung, and Blood Institute (NHLBI) sponsored study "Coronary Artery Risk Development in Young Adults" (CARDIA) provides a unique opportunity to examine the relationship between depression, body weight, and LVM as it is designed to increase understanding of contributors to changes in cardiovascular disease (CVD) risk factors during the critical years of transition from adolescence through young adulthood to middle age. This multi-site investigation utilized standardized measurements of major risk factors. In addition, psychosocial, dietary, and exercise-related characteristics that might influence these cardiovascular risk factors, or that might be independent risk factors, were assessed.

Proposed Pathway

Left ventricular mass (LVM) is known to be a powerful independent predictor for cardiovascular disease events in adults (Gardin et al., 2002). This information, when combined with the evidence that appears to link depressive symptoms to LVM, provides the rationale for choosing to investigate LVM as the mechanism through which depression increases CVD risk. If this mechanism is brought about through body weight, then body weight control should be a component of intervention strategies. Support for the proposed pathway in this study may indicate the possibility of decreasing CVD risk in depressed individuals by reversing LVH with weight loss.

The current study focused on a hypothesized pathway by which depression leads to an increased risk for cardiovascular disease. Specifically, this study examined LVM as a mechanism of the depression and cardiovascular disease association. To understand the concepts of LVM (Kop et al., 2000; Taylor et al., 2003) and depression (Musselman et al., 1998) as they relate to CVD, it is important to consider common variables that have been associated with both conditions. It is likely that the mechanisms linking depression and CVD are a combination of many processes. The hypothesized pathway to be studied in the current project is focused on one particular process, suggesting that the association between depression and LVM is mediated through body mass (See Figure 2).

The general hypothesis, supported by prior research, is that increases in body mass for depressed and non-depressed individuals will be correlated with increases in LVM. However, this study proposes that these effects will be most pronounced in the atypical depression group. It is hypothesized that in this study the atypical depression group will have the highest measures of body mass at baseline and will have the most

body mass gain over the course of the study. Based on the proposed pathway, the atypical depression group should also show the greatest increases in LVM over the course of the study. If body mass is an important mechanism linking depression to increased CVD morbidity and mortality risk (Ferketich et al., 2000), then this approach should allow for detection of the effect, through the relationship of depression-related body mass changes and LVM changes. The specific study hypotheses are:

1. The atypical depression subtype will have the highest measures of body mass at baseline.
2. Increases in body mass at all levels of depression will be correlated with increases in LVM over the 5-year follow-up period.
3. The atypical depression subtype will have the largest increase in body mass and LVM over the 5-year follow-up period.
4. The atypical depression subtype will account for the relationship between depression and LVM.
5. Body mass will act as a mediator between the atypical depression subtype and LVM.

Methods

The present study utilizes data from the Coronary Artery Risk Development in Young Adults (CARDIA) study (Cutter et al., 1991) to examine depression, body mass, and left ventricular mass. The CARDIA study is conducted and supported by the NHLBI in collaboration with the CARDIA Investigators. This thesis was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the CARDIA or the NHLBI. The initial objectives of CARDIA were: 1) To document levels and potential determinants of risk factors for CAD in young adults; 2) To study interrelationships of risk factors and lifestyles and to document behavioral and environmental changes during the transition from adolescence to middle age; 3) To compare cross-sectional and longitudinal data on age-related trends in CVD risk factors; and 4) To compare levels and progression of risk factors between men and women, African Americans and Caucasians, and between differing socioeconomic status levels. The sample was designed to achieve approximately balanced subgroups of race, gender, education, and age. CARDIA is a population-based observational study of 5,115 participants aged 18-30 when recruited in 1985-1986 from four urban areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota, and Oakland, California. The goals of the CARDIA evolved to emphasize understanding determinants of LVM and emerging obesity and hypertension, which made this data set optimal for the current investigation. The details of the CARDIA study design and characteristics of the participants have been previously described (Friedman et al., 1988; Cutter et al., 1991).

Of the total 4,351 available participants at Year 5 (55% male, 45% female, 49% African American, 51% Caucasian, mean age=29.95 ± 3.59), 1,433 were eligible for data analysis in this study. Participants were excluded when any of the three major variables for these analyses (depression, BMI, & LVM) were missing, in order to represent a sample that underwent comparative procedures and follow-up. At Year 5, 61 participants were excluded for missing CES-D score, 2,805 were excluded for no LVM measurement, and 4 were excluded for no BMI value. At Year 10, 44 participants were excluded for no LVM measurement and 4 were excluded for no BMI value. The final remaining sample of 1,433 participants included 789 females (55%), 644 males (45%), 852 Caucasians (59%), and 581 African Americans (41%) with an overall mean age of 30.08 ± 3.51. The demographics for this sample (n=1,433) were reasonably similar to those of the total available participants at Year 5 (n=4,351) suggesting that the sample used in this study was representative of the larger CARDIA study sample.

Measures

The CES-D Scale, administered at Year 5 of the CARDIA study, was used to assess depression (Radloff, 1977; Weissman et al., 1977; Myers & Weissman, 1980). The scale consists of 20 items with a four point Likert scale (1 = Rarely or none of the time, 2 = Some of the time, 3 = Much of the time, 4 = Most or all of the time). A total score of 16 or greater has been validated as sufficient for a diagnosis of depression and was used for this study (Comstock & Helsing, 1976; Ferketich et al., 2000). According to DSM-IV diagnostic criteria the "atypical features" specifier of depression is primarily characterized by 2 or more of the following symptoms: overeating, oversleeping, "leaden

paralysis", and interpersonal rejection sensitivity (APA, 1994). In order to separate those with atypical depression symptoms from those with typical depression symptoms, median splits were used for four items that exemplify the four atypical specifier symptoms. Items #2 ("I did not feel like eating: my appetite was poor"), #7 ("I felt that everything I did was an effort"), #11 ("My sleep was restless"), and #19 ("I felt that people disliked me") were used to determine specifier status. For items #2 and #11, a score of 1 or 2 was considered atypical, whereas for items #7 and #19, a score of 4 was considered atypical. To be classified as having atypical depression, an individual had to have a total score ≥ 16 and endorse, as described above, at least two of the four atypical items, one of which had to be #7 or #19. The reason for requiring item #7 or item #19 was that it was not absolutely clear that a score of 1 or 2 on items #2 and #11 was indicative of an atypical pattern (overeating and oversleeping) versus no disturbance. To be classified as having typical depression, an individual had to have a total score ≥ 16, a score of 3 or 4 on items #2 and #11, and a score below 4 on items #7 and #19. Any participant with a total score ≥ 16 who did not meet the criteria for either atypical or typical depression was removed from the analyses comparing subtypes of depression. Participants with a CES-D total score < 16 were classified as Not Depressed.

Although there is also a mood reactivity component in the DSM-IV atypical depression specifier definition (APA, 1994) it was not included in these analyses. There are several reasons for omitting this variable including the fact that the research model for this study was focused on more of the vegetative symptoms and not as much on the mood-related symptoms. In addition, the items of the CES-D were not conducive to

examining this variable whereas there were more parallels between the CES-D items and the four other atypical depression symptoms.

The other major variables in this study, body mass index (BMI) and left ventricular mass (LVM) were obtained from Year 5 and Year 10 of the CARDIA study. BMI was calculated as weight in kg divided by height in meters squared. LVM is an M-mode measure that was determined with echocardiography and computed by the CARDIA Coordinating Center through the following algorithm: 0.8 * (1.04 *(MMIVSTD+MMLVDD+MMLVPWD) * * 3) – MMLVDD * * 3 + 0.6. Other methods of determining LVM are available including the LVM index (LVMI), which controls for body surface area (Kop et al., 2000). The LVMI method was not utilized in the current study because of the importance of BMI in the research model and the preference for using the method used by the CARDIA study investigators. It was decided that controlling for body surface area would not allow for a comprehensive examination of the model. Patient report questionnaires were used to gather information on age, sex, race, education, smoking status, and hypertension diagnosis of the participants.

Statistical Analyses

SPSS for Windows (Version 11.5.0; SPSS Inc., Chicago, IL) was used to analyze the data. One-way ANOVAs were initially used to compare depression groups (Not depressed, Typical Depression, and Atypical Depression) on BMI, LVM, and continuous demographic measures. Repeated measures ANOVAs were used to examine change in BMI and LVM over time across depression groups. In addition, product-moment correlations were used to examine the relationships between continuous variables.

Analyses followed the methods of Baron & Kenny (1986) used to establish mediation. As is proposed in the present study, the following conditions must hold: the independent variable must affect the dependent variable, the independent variable must affect the mediator, and the mediator must affect the dependent variable (Baron & Kenny, 1986). In addition, perfect mediation occurs if the independent variable has no effect when the mediator is controlled for. To test the mediational model shown in Figure 2 a series of linear regression analyses were conducted with depression groups as the independent variable, LVM at Year 10 as the dependent variable, and BMI at Year 10 as the mediator. The first regression examined the effect of depression status on LVM at Year 10. The depression status variable was made up of two dummy coded variables comparing the Not Depressed group to the Atypical Depression group and to the Typical Depression group. In this first regression analysis, the two dummy coded depression variables examining depression groups were entered as the independent variable set and LVM at Year 10 was again the dependent variable. A third dummy coded variable was created to compare the Atypical Depression group to the Typical Depression group, and separate regressions were run with this variable in place of the Atypical Depression versus Not Depressed dummy coded variable.

The first regression analysis was designed to determine whether the independent variable affected the dependent variable. To determine whether the independent variable affected the mediator, the second regression entered the dummy coded depression group variables as the independent variable set and BMI at Year 10 as the dependent variable. The third regression examined if the mediator affected the dependent variable, with BMI at Year 10 entered in the regression model as the independent variable and LVM at Year

10 as the dependent variable. A final regression analysis was conducted on the effect of the independent variable (depression group dummy coded variables) on the dependent variable (LVM at Year 10) after controlling for the variance in LVM at Year 10 associated with the mediator (BMI at Year 10). In this analysis, BMI at Year 10 was entered as an independent variable, the depression group dummy coded variables were entered as the next independent variable set, and LVM at Year 10 was entered as the dependent variable.

Results

Sample Characteristics

The total N for this sample was 1433, and the sample characteristics by depression group are presented in Table 1. Of the 1433 participants analyzed in the study, there were 1094 in the Not Depressed group, 90 in the Atypical Depression group, and 94 in the Typical Depression group. One hundred fifty-five participants who had a CES-D score greater than or equal to 16 were excluded because they did not meet criteria for the Atypical or Typical Depression groups. As expected, CES-D scores were significantly higher in the Atypical Depression and Typical Depression groups than in the Not Depressed group ($p<0.001$). In addition, the Atypical Depression group scored a few points higher on the CES-D than the Typical Depression group ($p<0.05$). Although the depression groups were comparable in age, there were substantially more individuals in the Not Depressed group, the Not Depressed group had approximately one year more of education than the Atypical Depression and Typical Depression groups ($p<0.001$ &

p<0.01 respectively), and the groups differed in racial and sex profiles. There were significantly more whites than blacks (X^2 [1]=87.84, p<0.001) and marginally more females than males (X^2 [1]=3.29, p=0.070) in the Not Depressed group. The Typical Depression group had significantly more blacks than whites (X^2 [1]=8.34, p=0.004) and females than males (X^2 [1]=13.79, p<0.001). Lastly, there were significantly more blacks than whites (X^2 [1]=3.60, p=0.058) in the Atypical Depression group, but no difference in sex (X^2 [1]=2.18, p=0.140).

Hypothesis One: Atypical Depression and BMI at Baseline

Table 2 lists the BMI and LVM values for Years 5 and 10 by depression group. As hypothesized, the Atypical Depression group had the highest BMI at baseline, which was significantly different from the Not Depressed group ($p < 0.001$).

To allow for exploration of possible interactions in the effects of depression with race and sex, variables shown to be important to LVM, a univariate ANOVA revealed a three-way interaction of sex, race, and depression group (F[2,1266]=4.18, p=0.016). Therefore, all hypotheses were analyzed first in the overall sample and then separately for race-by-sex groups including: black males, black females, white males, and white females. Results indicated that Hypothesis 1 held only for whites (F[2,768]=4.28, p=0.01), but not blacks (F[2,504]=1.78, p=0.17), with the Atypical Depression group having higher baseline BMI values than both the Typical Depression group (p=0.021) and the Not Depressed group (p=0.021). Values of BMI and LVM for Year 5 and 10 by race, sex, and depression group are presented in Table 3. For black males and black females there was no depression group difference in BMI at baseline (F[2,206]=0.79,

p=0.46 and F[2,295]=1.36, p=0.26 respectively). However, there was a marginal effect of depression group on baseline BMI in both the white males and white females (F[2,372]=2.52, p=0.08 and F[2,393]=2.83, p=0.06 respectively). For white females the Atypical Group had the highest baseline BMI as hypothesized and were significantly different from the Not Depressed group (p=0.047). In white males, the Atypical Depression group also had the highest BMI at baseline, but were different from the Typical Depression group (p=0.068).

Hypothesis Two: Increases in BMI and LVM

BMI at Year 5 was positively correlated with LVM at Year 5 ($r = 0.36$, $p<0.001$) and BMI at Year 10 was positively correlated with LVM at Year 10 ($r = 0.38$, $p<0.001$). Change scores from Year 5 to Year 10 were calculated for BMI (1.27 ± 2.37) and LVM (1.04 ± 22.62). The change in BMI across the entire sample was significantly correlated with the change in LVM ($r = 0.21$, $p < 0.001$). As hypothesized, these two variables were positively correlated indicating increases in BMI over time were related to increases in LVM (Figure 3).

BMI at Year 5 was positively correlated with LVM at Year 5 for all race-by-sex groups ($p<0.001$) and BMI at Year 10 was positively correlated with LVM at Year 10 for all race-by-sex groups ($p<0.001$). Hypothesis two was analyzed across race-by-sex groups. Correlational analysis indicated there was a positive correlation for each group. All four comparisons were significant, but the strongest correlation was found for the black females ($r=0.32$, $p<0.001$).

Hypothesis Three: Increases in BMI and LVM by Depression Group

The changes in BMI and LVM from Year 5 to Year 10 across depression groups are presented in Figures 4 and 5 respectively. There was a significant increase in BMI from Year 5 to Year 10 regardless of depression group ($F[1,1275]=135.60$, $p<0.001$). In addition there was a main effect for depression group ($F[2,1275]=9.66$, $p<0.001$), such that BMI was greater in the atypical depression group than the not depressed group ($p<0.001$). However, contrary to expectations, the interaction of time and depression group was not significant, indicating that no depression group increased more in BMI than another ($F[2,1275]=0.79$, $p=0.455$).

The results for LVM are similar to those of BMI. A significant main effect of time was observed for the LVM increase from Year 5 to Year 10 ($F[1,1275]=4.04$, $p=0.045$). There was also a significant effect of depression group ($F[2,1275]=3.58$, $p=0.028$), such that LVM was greater in the atypical depression group than the typical depression group ($p=0.026$). However, as with the BMI analyses, there was no significant interaction of time and depression group for LVM ($F[2,1275=1.12$, $p=0.331$).

Changes in BMI and LVM from Year 5 to Year 10 across depression groups were examined among race-by-sex groups. For all four groups (BM, BF, WM, WF) BMI significantly increased from Year 5 to Year 10 regardless of depression group ($p<0.001$). There was a main effect of depression group only in the white male group ($F[2,372]=2.96$, $p=0.05$), with the Atypical Depression group significantly higher than the Typical Depression group ($p=0.045$). As with the overall analyses, no interaction of time and depression group for BMI was found.

The results for subgroup changes in LVM from Year 5 to Year 10 are different than for change in BMI. LVM significantly increased from Year 5 to Year 10 regardless of depression group in the black female group only ($F[1,295]=15.72$, $p<0.001$). The main effect of depression was only significant in the white male group ($F[2,372]=4.18$, $p=0.016$) with the Atypical Depression group significantly higher than the Typical Depression group ($p=0.012$). No interaction of time and depression group was observed for LVM.

Hypothesis Four: Atypical Depression and LVM

The hypothesis that the relationship between depression and LVM would be accounted for by Atypical Depression was tested via regression. These analyses revealed a trend toward higher LVM at Year 10 associated with depression status ($F[2,1275]=2.587$, $p=0.076$). Further analyses utilizing the dummy coded variables for depression group determined that the variable that compared Atypical Depression to Not Depressed did not significantly predict LVM at Year 10 ($B=6.12$, $p=0.172$) and the variable comparing Typical Depression to Not Depressed only marginally predicted LVM at Year 10 ($B=-7.48$, $p=0.088$). Unexpectedly, the variable that represented the comparison of the Atypical Depression group to the Typical Depression group did significantly predict LVM at Year 10 ($B=13.60$, $p=0.024$).

In race-by-sex analyses, depression status at Year 5 significantly affected LVM at Year 10 for the white males only ($F[2,372]=4.761$, $p=0.009$). For the white males, the variable comparing Atypical Depression to Not Depressed and the variable comparing Typical Depression to Not Depressed both significantly affected LVM at Year 10

(B=19.01, p=0.037 & B=-27.14, p=0.028 respectively). In addition, the variable comparing Atypical Depression to Typical Depression also significantly affected LVM at Year 10 (B=46.15, p=0.002). Further analyses across the race-by-sex groups revealed that in black females, although the overall effect of depression status was not significant, the dummy coded variable comparing Atypical Depression to Not Depressed significantly affected LVM at Year 10 (B=13.38, p=0.042) whereas the variable comparing Typical Depression to Not Depressed and the variable comparing Atypical Depression to Typical Depression did not significantly affect LVM at Year 10 (B=3.99, p=0.496 and B=9.39, p=0.251 respectively). No significant relationships were found for black males or white females. A graphical representation of these race-by-sex results is presented in Figure 6.

Hypothesis Five: BMI as a Mediator

As described in the Methods section, to test Hypothesis 5 a series of regression analyses were conducted to investigate the mediational model proposed in Figure 2. These analyses were aimed at determining whether the independent variable (depression group) affected the dependent variable (LVM at Year 10), the independent variable affected the mediator (BMI at Year 10), and the mediator affected the dependent variable (Baron & Kenny, 1986). First, it was determined that the dummy coded variable that compared Atypical Depression to Typical Depression significantly predicted LVM at Year 10 (p=0.002). The second regression found that Depression group significantly affected BMI at Year 10 ($F[2,1275]=9.49$, $p<0.001$), such that the Atypical Depression vs. Typical Depression dummy coded variable significantly predicted BMI at Year 10 (B=1.58, p=0.056). The mediator, BMI at Year 10, significantly affected LVM at Year 10

(F[1,1276]=208.98, p<0.001) in the third regression analysis. The final regression analysis examined the mediational model in its entirety and found that when BMI at Year 10 was controlled for, the Atypical Depression vs. Typical Depression dummy coded variable no longer significantly affected LVM at Year 10 (B=9.27, p=0.097). However, the Typical Depression vs. Not Depressed dummy coded variable became significantly predictive of LVM at Year 10 (B=-10.15, p=0.013) after controlling for BMI at Year 10.

Regression analyses across the race-by-sex groups revealed that in the black females the Atypical Depression vs. Not Depressed dummy coded variable significantly affected LVM at Year 10 (p=0.042) whereas the Typical Depression vs. Not Depressed variable did not significantly affect LVM at Year 10 (p=0.496). In white males, the Atypical Depression vs. Not Depressed dummy coded variable and the Typical Depression vs. Not Depressed variable both significantly affected LVM at Year 10 (p=0.037 & p=0.028 respectively). No significant relationships were found for black males or white females. Therefore, the remainder of the mediational analyses will only be reported for the black female and white male groups. The second regression analysis showed that depression group significantly affected BMI at Year 10 for the white males (F[2,372]=3.04, p=0.049), but not for the black females (F[2,295]=1.96, p=0.143). However, the comparison of Atypical Depression to Not Depressed marginally affected BMI at Year 10 for the black females (B=2.55, p=0.068). In the white male group the Atypical Depression vs. Not Depressed dummy coded variable marginally affected BMI at Year 10 (B=1.74, p=0.072), the Atypical Depression vs. Typical Depression variable significantly affected BMI at Year 10 (B=3.87, p=0.016), but the Typical Depression vs. Not Depressed dummy coded variable was not significantly related to BMI at Year 10

(B=-2.13, p=0.104). For both the black females and white males, the third regression analysis indicated that BMI at Year 10 significantly affected LVM at Year 10 (F[1,296]=140.69, p<0.001 and F[1,373]=84.00, p<0.001 respectively). The final regression analysis tested the entire mediational model. For black females, when the variance associated with BMI at Year 10 was controlled none of the comparisons between depression groups significantly affected LVM at Year 10, including the variable comparing Atypical Depression to Not Depressed (B=6.66, p=0.223).

In summary, in the white male group, after controlling for BMI at Year 10 both Atypical Depression vs. Not Depressed and Typical Depression vs. Not Depressed were no longer significantly associated with LVM at Year 10 (B=12.17, p=0.143 and B=-18.78, p=0.096 respectively) whereas the variable comparing Atypical Depression to Typical Depression remained significantly related to LVM at Year 10 (B=30.95, p=0.026) with higher LVM for the Atypical Depression group. The mediational regression analyses revealed that hypothesis five was supported for the black females and white males because BMI at Year 10 mediated the relationship of the Atypical Depression subtype to LVM at Year 10.

Blood Pressure as a Mediator

In order to investigate the possibility that blood pressure could also act as a mediator between depression group and LVM, another series of regression analyses was conducted. Systolic (SBP) and diastolic (DBP) blood pressure at Year 10 were analyzed as mediators utilizing the methods of Baron & Kenny (1986) for assessing mediators. The regression analysis results comparing the independent variable (depression status/group)

with the dependent variable (LVM at Year 10) are presented with the Hypothesis Four results, indicating that the dummy coded variable that compared Atypical Depression to Typical Depression significantly predicted LVM at Year 10 ($p=0.002$). The second regression found that Depression group significantly affected SBP at Year 10 ($F[2,1275]=5.26$, $p=0.005$), such that the Atypical Depression vs. Typical Depression dummy coded variable significantly predicted SBP at Year 10 ($B=3.58$, $p=0.035$). There was no relationship between depression group and DBP at Year 10 ($F[2,1275]=0.93$, $p=0.394$). Therefore, DBP at Year 10 was not analyzed further in the mediational model. The mediator, SBP at Year 10, significantly affected LVM at Year 10 ($F[1,1276]=234.41$, $p<0.001$) in the third regression analysis. The final regression analysis examined the mediational model in its entirety and found that when SBP at Year 10 was controlled for, the Atypical Depression vs. Typical Depression dummy coded variable no longer significantly affected LVM at Year 10 ($B=8.61$, $p=0.121$). However, the Typical Depression vs. Not Depressed dummy coded variable became significantly predictive of LVM at Year 10 ($B=-8.19$, $p=0.043$) after controlling for SBP at Year 10. These results indicate that SBP at Year 10 acts as a complete mediator for Atypical Depression as compared with Typical Depression just as BMI at Year 10 did in the overall hypothesis five analyses. A final regression found that when both BMI at Year 10 and SBP at Year 10 were entered as separate sets in the model, each served as an independent mediator between Atypical Depression and LVM at Year 10 because both variables contributed uniquely to the total variance in LVM at Year 10 explained by the independent variables. Figure 7 uses the data from this study to replicate the graphs found in Schirmer et al. (1999) and in Figure 1 in this paper.

The relationship of blood pressure to depression groups and LVM was examined across race-by-sex group. Results from the regression analyses presented in Hypothesis Four in each of the race-by-sex groups revealed that in the black females the Atypical Depression vs. Not Depressed dummy coded variable significantly affected LVM at Year 10 ($p=0.042$) whereas the Typical Depression vs. Not Depressed variable did not significantly affect LVM at Year 10 ($p=0.496$). In white males, the Atypical Depression vs. Not Depressed dummy coded variable and the Typical Depression vs. Not Depressed variable both significantly affected LVM at Year 10 ($p=0.037$ & $p=0.028$ respectively). No significant relationships were found for black males or white females. The second regression analysis showed that depression status significantly affected SBP at Year 10 for the white females ($F[2,393]=3.17$, $p=0.043$) and marginally for the black females ($F[2,295]=2.76$, $p=0.065$). In the white female group, the dummy coded variable comparing Atypical Depression to Not Depressed was significantly associated with SBP at Year 10 ($B=4.11$, $p=0.054$), but the variable comparing Typical Depression to Not Depressed was not significantly associated with SBP at Year 10 ($B=3.38$, $p=0.085$). For the black females the Atypical Depression vs. Not Depressed dummy coded variable was significantly associated with SBP at Year 10 ($B=5.36$, $p=0.035$), but the Typical Depression vs. Not Depressed variable did not significantly affect SBP at Year 10 ($B=-1.61$, $p=0.476$). Again, there were no significant associations between depression group and DBP at Year 10 for any race-by-sex group. Therefore, DBP at Year 10 was not analyzed further in the mediational model.

Because the only significant association between the independent and dependent variables was found for the black female group, the remainder of the mediational

analyses will be reported for the black female group only. In this group, regression analysis indicated that SBP at Year 10 significantly affected LVM at Year 10 ($F[1,296]=55.89$, $p<0.001$). The final regression analysis tested the entire mediational model for black females. When the variance associated with SBP at Year 10 was controlled neither dummy coded variable (Atypical Depression vs. Not Depressed or Typical Depression vs. Not Depressed) significantly affected LVM at Year 10 ($B=7.94$, $p=0.192$ and $B=5.63$, $p=0.298$ respectively).

In sum, the mediational regression analyses revealed that the notion regarding blood pressure as a mediator was only supported for the black female group with Atypical Depression. Otherwise this hypothesis was not supported for any of the other race-by-sex groups. In the case of black males and white females, the independent variable (depression group) was not associated with the dependent variable (LVM at Year 10). Whereas for the white males, the independent variable (depression group) was associated with the dependent variable (LVM at Year 10), but the independent variable was not associated with the mediator (SBP at Year 10). A final regression for black females found that when both BMI at Year 10 and SBP at Year 10 were entered as separate sets in the model, each served as an independent mediator between Atypical Depression and LVM at Year 10 because both variables contributed uniquely to the total variance in LVM at Year 10 explained by the independent variables.

Other Analyses

In addition to the analyses conducted to examine the original hypotheses, a number of exploratory questions were also investigated. The first of these analyses tested

whether there were differences in the depression to LVM relationship between those who were depressed at Year 5 and Year 10 versus those who were depressed at Year 5 only. Although the Year 10 LVM for those with sustained depression was higher than for the temporarily depressed individuals ($\bar{X}$ =145.16±42.61 vs $\bar{X}$ =137.89±40.37), a *t*-test comparing these two groups on Year 10 LVM found no significant difference (*t*=1.59, p=0.114).

The second exploratory analysis conducted was an item analysis to determine the predictive value of each item on the CES-D to Year 10 LVM. For the overall sample the following relationships were found: "Everything I did was an effort" was positively predictive (B=2.98, p=0.020), "I felt fearful" was negatively predictive (B=-3.60, p=0.047), "Talked less than usual" was positively predictive (B=3.44, p=0.019), "I enjoyed life" was positively predictive (B=2.51, p=0.049), "I had crying spells" was negatively predictive (B=-10.09, p<0.001), and "I felt sad" was negatively predictive (B=-3.20, p=0.06). For the depressed portion of the sample the following relationships were found: "My appetite was poor" was negatively predictive (B=-4.89, p=0.08), "Everything I did was an effort" was positively predictive (B=4.57, p=0.095), "I felt fearful" was negatively predictive (B=-5.28, p=0.068), "Talked less than usual" was positively predictive (B=6.85, p=0.011), "I enjoyed life" was positively predictive (B=7.44, p=0.008), and "I had crying spells" was negatively predictive (B=-11.36, p<0.001). Due to the increased risk of Type I error with so many comparisons (20 items on the CES-D) and the lack of a clear pattern, the evidence regarding CES-D item predictability of LVM is inconclusive and any explanations would be exceedingly speculative.

Discussion

Summary of Results

This study demonstrates that depression status at Year 5 was associated with a substantial proportion of the variance in left ventricular mass at Year 10. It was further determined that atypical depression status compared with typical depression accounted for the relationship between depression and LVM in the overall sample. Atypical depression was also associated with higher BMI, and in turn BMI was found to mediate the relationship between atypical depression as compared to typical depression and LVM. There was no interaction of time by depression group for BMI or LVM indicating all groups increased similarly although the atypical depression group was higher at both time points. Although not originally hypothesized, systolic blood pressure also acted as a mediator between atypical depression as compared to typical depression and LVM, independent of body mass.

However, the overall analyses were not a full representation of the relationships involved in this data set because there were other variables that had an important impact. Analyses examining variables important to LVM revealed a three-way interaction of sex, race, and depression group. Therefore, all hypotheses were reanalyzed across a combined sex-by-race variable. It appears that Hypotheses 4 (atypical depression would account for the relationship of depression and LVM) and 5 (BMI would mediate relationship between atypical depression and LVM) were supported in black females, such that the Atypical Depression group had significantly higher LVM at Year 10 than the Not Depressed group. In addition, BMI mediated the relationship between atypical depression as compared to not depressed and LVM in black females. For white males, Hypothesis 4

was not supported because both atypical and typical depression were significantly associated with LVM at Year 10 (significantly higher and lower respectively as compared to the Not Depressed group). Hypothesis 5 was supported in the white male group because BMI at Year 10 mediated the relationship between Atypical Depression as compared to Not Depressed and LVM at Year 10. However, the relationship between Typical Depression as compared to Not Depressed and LVM Year 10 was also mediated by BMI at Year 10, which was not originally hypothesized because typical depression was not expected to be significantly associated with LVM.

Depression, LVM, and CVD

The finding that LVM varies as a function of depression subtypes has implications for the mechanism(s) by which depression may act as a CVD risk factor. Because atypical depression was associated with significantly higher LVM at Year 10 than typical depression, it appears that the symptom profile specific to the atypical depression subtype confers negative health consequences. These analyses provide evidence that the negative impact of increased body mass from overeating and lack of energy could explain most of the relationship between atypical depression and LVM, which is a marker of future CVD. Although future CVD occurrence was not examined in the present analyses, it is supposed that increases in LVM would translate into increased risk of CVD over time (Sharp & Mayet, 2002; Dei Cas et al., 2003). Therefore, LVH may act as a mechanism to explain the increased CVD risk that is associated with depression (Frasure-Smith et al., 1995; Wulsin & Singal, 2003). This mechanism may only hold for the atypical depression subtype, but it is unclear from these analyses if that is the case.

An unexpected finding was that the Typical Depression group had smaller LVM than the Not Depressed group. Although atypical depression was hypothesized to account for the association of depression and LVM, it was assumed that both depression groups would have higher LVM than those who were not depressed. A potential explanation for smaller LVM in the Typical Depression group as a result of cortisol levels was explored. There is evidence that sleep loss is associated with temporal cortisol elevation and dysregulation (Brown et al., 2004). The fact that typical depression is associated with insomnia suggests that this subtype of depression may be more prone to cortisol elevations. Perhaps the typical depression group had a higher proportion of hypothalamic–pituitary–adrenal (HPA) axis dysregulated individuals leading to higher cortisol levels. Elevations in cortisol during depressive episodes have been thought of as part of the etiology of the association between major depressive disorder and systemic illness, and perhaps even mild increases in cortisol may have health consequences (Brown et al., 2004). There is also evidence that glucocorticoids induce rapid muscle breakdown and proximal muscle atrophy as a result of degradation of the myosin heavy chain (Salehian & Kejriwal, 1999). It is possible that typical depression was associated with smaller LVM because of cardiac muscle degradation as a result of HPA axis dysregulation and increased cortisol levels. This evidence suggests a revision to the hypothesis regarding the health consequences and CVD risk from subtypes of depression, such that there may be different mechanisms generating risk. For atypical depression, the mechanism could be related to changes in the body as a result of atypical specific symptoms, such as increased body mass and SBP. In contrast, the mechanism for typical

depression could be related to HPA axis dysregulation and the associated effects in the body.

Blood Pressure as a Mediator

The results of the blood pressure mediational analyses were important because they verified that although SBP is an important mediating factor between depression and LVM, there is still an independent contribution of BMI to the overall variance of LVM. It appears that as previously reported (Gardin et al., 2002) both body mass and blood pressure have a significant impact on LVM. The strength of these two variables as mediators differs across depression subtypes and race-by-sex groups. It is probable that the relationship of depression to CVD through LVM may have several mediators depending on the group and subtype of depression under examination. The most important outcome of the blood pressure mediational results is that it ruled out the possibility that the effects of blood pressure were entirely responsible for the mediational effects of body mass.

Role of Sex and Race

Based on the results of this study there seems to be evidence that sex and race are both important variables in the study of depression and left ventricular mass. Research regarding the relationship of race, sex, and depression has found that depression is more common in whites and women (Zhang & Snowden, 1999; Lucht et al., 2003). There is evidence to the contrary as well, showing a higher prevalence of depression in blacks than whites, although this reversal was attributed to greater health burdens and lack of

health insurance in minorities (Dunlop et al., 2003). Evidence from previous literature also supports a relationship between race, sex, and left ventricular mass and hypertrophy with left ventricular hypertrophy more common in women and in blacks (Savage et al., 1979; Liao et al., 1995). This support extends to race and sex differences in risk and survival associated with left ventricular mass and hypertrophy (East et al., 2003). It is noteworthy that in the current study, analyses for women (both black and white) did not yield conclusive results regarding the relationship of depression and left ventricular mass, although previous work has indicated a higher prevalence of both depression and left ventricular hypertrophy in women. The inconclusiveness of these results may be attributable to the underpowered nature of the analyses.

There is evidence that not only do blacks and whites present differently with depression (Harris, 2004), but there may be important differences in their responses to the CES-D in particular. Analyses by Iwata and colleagues (2002) found that approximately half of the items on the CES-D functioned differently for whites as compared to other racial/ethnic groups. More specifically, there were certain items on the CES-D that whites tended to over- or under-endorse as compared to the other groups. The authors report that blacks under-endorsed the "sad" item and over-endorsed the "effort" item, which corresponds to previous reports of blacks favoring somatic symptoms over depressive ones (Brown et al., 1996). It is possible that the results in the current study are a result of the way that different ethnic groups respond to the CES-D questions and specifically those items that went into creating the atypical depression specifier in this study. If the CES-D was not capturing depression similarly for black and white participants in the

CARDIA study, then it may not be appropriate to make comparisons of the associations between depression subtypes and LVM across races.

This study provides an initial look into the association of race and sex with depression and left ventricular mass. However, other researchers have examined race, sex, risk factor associations with markers and endpoints other than LVM. A follow-up analysis of the ENRICHD data by Schneiderman and colleagues (2004) presented an example from the ENRICHD study of the differing effects of race-by-sex sub-groups on CBT depression treatment for cardiovascular endpoints. As in the present study, only the white male sub-group appeared to have a strong association between depression/depression treatment and cardiovascular morbidity and mortality outcome. It could be speculated that part of the treatment efficacy found for white males in the Schneiderman et al. (2004) study could be due to the relationship of depression and left ventricular mass evident in the current study for white males. Furthermore, it could be that depression subtype and treatment of atypical symptoms in the white males led to a decrease in body mass and blood pressure, which in turn reduced their left ventricular mass and cardiovascular disease risk. It is not clear why similar treatments would not be successful for the other three race-by-sex sub-groups, except that perhaps the lack of a relationship between subtypes of depression and LVM in those groups prevents treatment efficacy that is as successful as for white men.

Study Limitations

Interpretation of these analyses is limited by a number of factors. Although the full sample size available from the CARDIA study was substantial, after excluding based

on missing values and categorizing based on depression subtypes, the sample size for this study was reduced and unbalanced. The original sample consisted of 4,351 participants, but was reduced to 1,433. Analyses did indicate that the smaller sample used for this study was relatively comparable in demographic characteristics to the larger CARDIA sample. However, there may have been valuable information from the 2,918 participants excluded from these analyses. Although the atypical (n=90) and typical (n=94) depression groups were similar in terms of sample size, the non-depressed group was considerably larger (n=1094). This imbalance in sample size between the groups could present a problem with uneven weighting. Optimally, participants would be recruited in future studies for a specific research design similar to the current study, which would help to reduce the imbalance in groups.

A second limitation is that the CES-D scale does not have a validated atypical depression specifier scale. The source of data for the present analyses was the CARDIA study, which included the CES-D to measure depression. In order to utilize the data available from the CARDIA study, a scoring procedure was developed for this study based on DSM-IV (APA, 1994) criteria to separate participants into atypical and typical depression subtypes. This method has not been validated, which limits the accuracy of the interpretations made from these analyses. As an exploratory study utilizing previously collected accessible data from other investigators, compromises are inevitable. The results of this study highlight important areas to be examined more rigorously, such as the differential effect of atypical and typical depression on LVM and the role of LVM as a mechanism between depression and CVD risk. If the importance of distinguishing between different subtypes of depression is corroborated by future research, then it would

be useful for investigators to develop and validate methods of categorizing those subtypes from the current most frequently used measures of depression.

Finally, it is possible that because the CARDIA study was conducted on relatively young and healthy individuals, the data were not completely conducive to looking into relationships with left ventricular mass and its changes over time. Perhaps an older, but similarly diverse and relatively healthy sample could provide additional information regarding the nature of these results. In addition, a five year time period may not be long enough to show significant changes in LVM, especially in this sample of healthy, young individuals. In fact, significant changes in LVM were only found in the black females. It is possible that more time is required to maximize the effects of depression on LVM. The 15-year follow-up in the CARDIA study includes data on the change in LVM and other factors over the course of ten years, which could provide a valuable source for further analyses.

Study Implications

This study was aimed at investigating a possible mechanism between depression and CVD. However, these analyses were limited to the relationship between depression and LVM without examining cardiovascular disease outcomes. Any implications regarding LVM as a mechanism to explain the increased CVD risk associated with depression are based on the literature that depicts increases in LVM as a marker of CVD (Gardin et al., 2002). Future studies should be conducted to examine the CVD end points along with the model investigated in this study. Without information on future CVD

occurrence, the results from this study only suggest the possibility for LVM as a mechanism.

Given the limitations for generalization, the findings from this study suggest that not only is distinguishing subtypes of depression a potentially important element of determining CVD risk from LVM, but that race-by-sex groups contribute to determining that risk. The evidence that implicates a relationship between depression subtypes and LVM is strongest in white males, but there is potential for these relationships in other race-by-sex groups. Future research is implicated to more fully determine if there are differential associations between depression subtypes and LVM. Further, if these associations exist, research that incorporates adequate sample size in a diverse population could be conducted to investigate whether LVM acts as a mediator between depression and CVD similarly across race and sex. Several future studies are recommended to detail the role of subtypes of depression in left ventricular mass across race and gender, as well as an integration of these concepts with depression subtype-specific treatment trials. In addition, research into interventions designed to detect and treat depression in its earliest stages are important, including those that may specifically protect the body from the damaging effects of increased body mass, blood pressure, and cortisol (Brown et al., 2004).

Table 1: Sample demographics

	Not Depressed	Atypical Depression	Typical Depression
N	1094	90	94
Age	30.14 ± 3.49	29.71 ± 3.63	30.15 ± 3.48
Female (%)	577 (53)	52 (58)	65 (69)
Caucasian (%)	702 (64)	36 (40)	33 (35)
African American (%)	392 (36)	54 (60)	61 (65)
Years of Education [*] [+]	14.39 ± 2.01	13.41 ± 1.96	13.68 ± 1.94
Smoker (%)	340 (31)	40 (44)	43 (46)
CES-D Score [*] [^] [#]	7.63 ± 4.07	23.43 ± 6.40	21.35 ± 4.95
Year 5 SBP (mm Hg)	105.75 ± 10.62	107.47 ± 13.34	106.22 ± 10.42
Year 5 DBP (mm Hg)	66.31 ± 9.48	67.44 ± 10.22	67.43 ± 9.10
Year 10 SBP (mm Hg)	107.76 ± 11.29	111.84 ± 12.89	108.27 ± 12.42
Year 10 DBP (mm Hg)	69.77 ± 9.95	71.27 ± 10.71	69.91 ± 9.37
Hypertension Dx (%)	63 (6)	15 (17)	7 (7)

[*] $p < 0.001$ Atypical vs. Not Depressed
[+] $p < 0.01$ Typical vs. Not Depressed
[^] $p < 0.001$ Typical vs. Not Depressed
[#] $p < 0.05$ Atypical vs. Typical

Table 2: BMI and LVM by depression groups (mean ± standard deviation)

	Not Depressed	Atypical Depression	Typical Depression	Total
N	1094	90	94	1278
BMI Year 5 * (kg/m^2)	25.29 ± 4.85	27.53 ± 6.37	26.15 ± 6.20	25.51 ± 5.11
BMI Year 10 * (kg/m^2)	26.53 ± 5.45	29.08 ± 6.61	27.50 ± 6.37	26.78 ± 5.64
LVM Year 5 + (g)	139.38 ± 39.49	144.20 ± 41.90	128.42 ± 34.87	138.91 ± 39.44
LVM Year 10 # (g)	140.07 ± 41.02	146.19 ± 43.30	132.58 ± 35.43	139.95 ± 40.86

BMI=body mass index; LVM=left ventricular mass

* $p < 0.001$ Atypical vs. Not Depressed

+ $p < 0.05$ Atypical vs. Typical & Typical vs. Not Depressed

$p = 0.06$ Atypical vs. Typical

Table 3: BMI by race, sex, and depression groups (mean ± standard deviation)

				BMI Year 5		BMI Year 10	
			N	Mean	SD	Mean	SD
Males	Black	Not Depressed	165	26.21	4.35	27.47	5.14
		Typical Depression	21	25.78	4.72	26.68	5.10
		Atypical Depression	23	27.33	5.09	28.81	4.96
	White	Not Depressed	352	25.13	3.34	26.14	3.69
		Typical Depression	8	23.21	1.19	24.01	1.71
		Atypical Depression	15	26.48	4.26	27.88	3.76
Females	Black	Not Depressed	227	27.16	6.84	28.77	7.21
		Typical Depression	40	28.34	7.67	30.00	7.23
		Atypical Depression	31	29.13	8.01	31.32	7.89
	White	Not Depressed	350	23.79	4.28	25.03	5.20
		Typical Depression	25	23.89	4.27	25.31	5.43
		Atypical Depression	21	26.13	6.00	26.94	7.11

BMI=body mass index (kg/m^2); LVM=left ventricular mass (g)

Table 4: LVM by race, sex, and depression groups (mean ± standard deviation)

				LVM Year 5		LVM Year 10	
			N	Mean	SD	Mean	SD
Males	Black	Not Depressed	165	174.30	39.47	175.05	42.91
		Typical Depression	21	162.56	31.39	166.95	40.19
		Atypical Depression	23	171.77	39.59	166.96	36.21
	White	Not Depressed	352	160.17	33.12	159.18	33.75
		Typical Depression	8	140.25	18.28	132.04	24.52
		Atypical Depression	15	173.69	37.03	178.19	51.67
Females	Black	Not Depressed	227	120.36	29.06	124.38	35.27
		Typical Depression	40	120.29	30.33	128.37	28.38
		Atypical Depression	31	128.75	30.19	137.75	32.23
	White	Not Depressed	350	114.33	24.99	114.53	26.32
		Typical Depression	25	108.96	26.96	110.63	21.68
		Atypical Depression	21	115.74	31.82	113.02	30.74

BMI=body mass index (kg/m^2); LVM=left ventricular mass (g)

Figure 1: Age-adjusted sex-specific prevalences of left ventricular hypertrophy plotted against quintiles of body mass index (BMI) and systolic blood pressure (SBP) in subjects without a history of cardiovascular disease (Schirmer et al., 1999).

▽ = men; ▲ = women

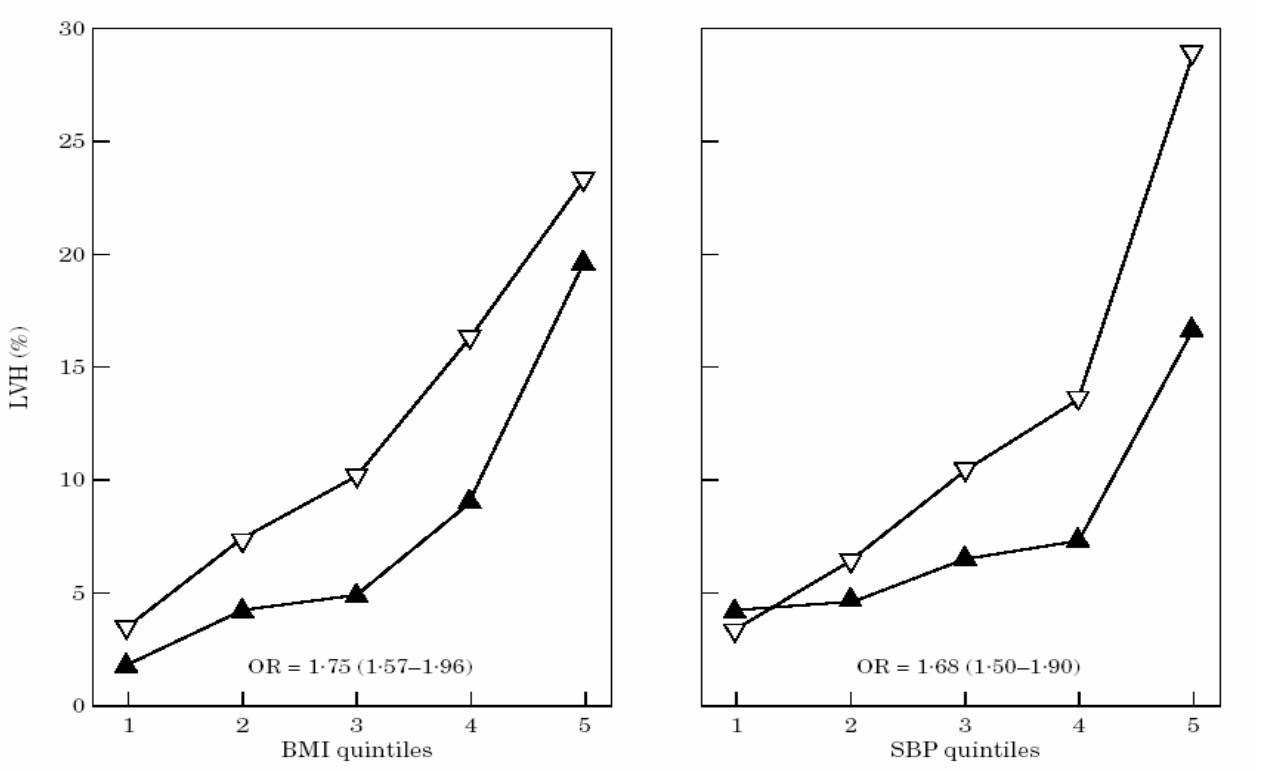


Figure 2: Theoretical model linking depression to LVM through body mass

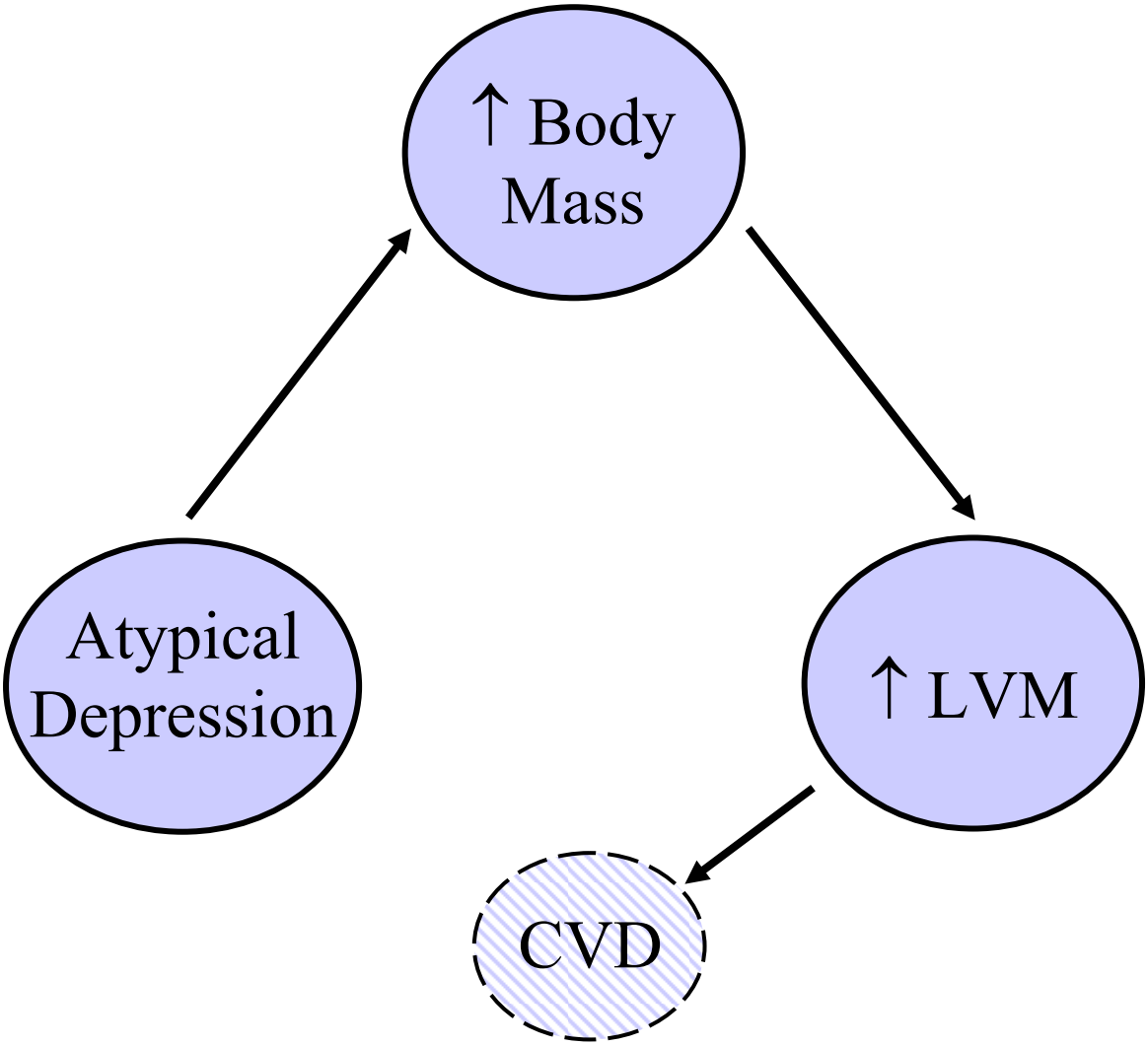


Figure 3: Change in body mass index versus change in left ventricular mass over 5 years

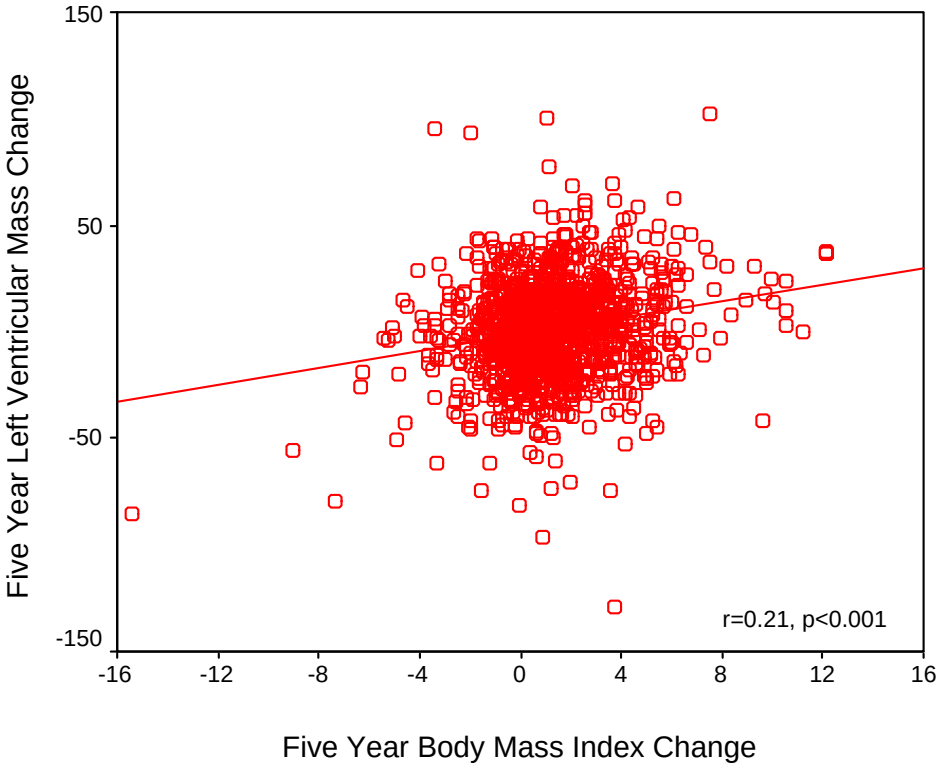


Figure 4: Change in Body Mass Index Over Time Across the Three Depression Groups (Mean ± SE)

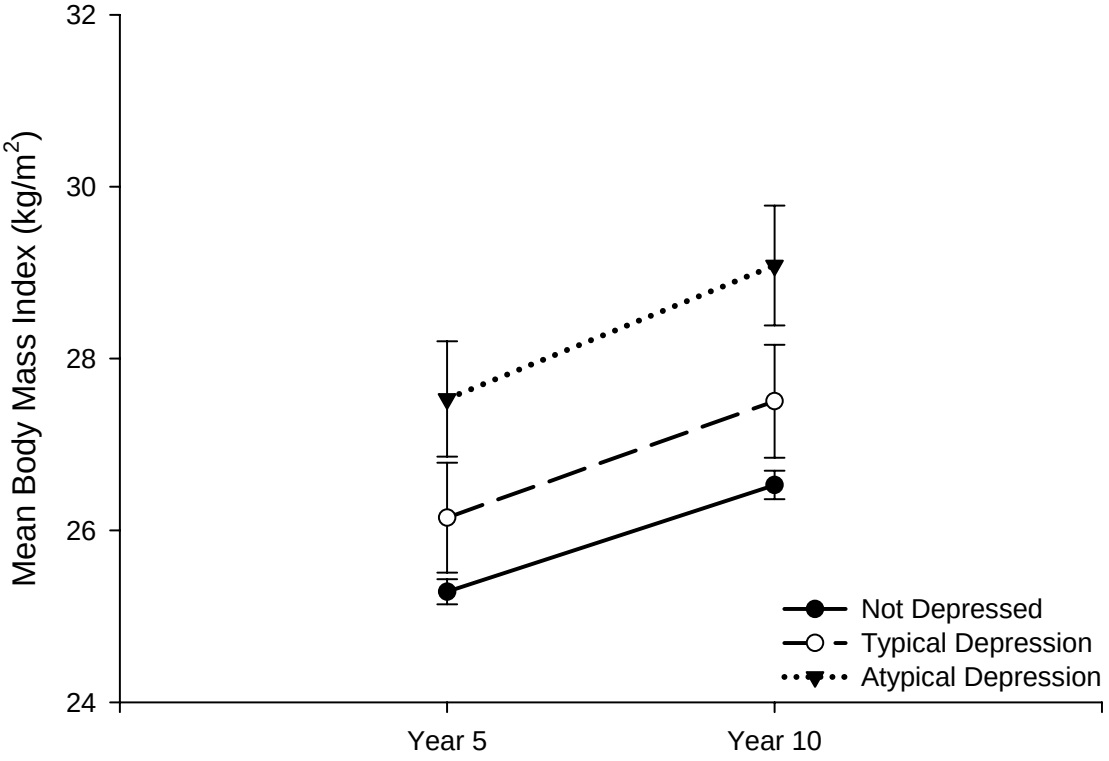


Figure 5: Change in Left Ventricular Mass Over Time Across the Three Depression Groups (Mean ± SE)

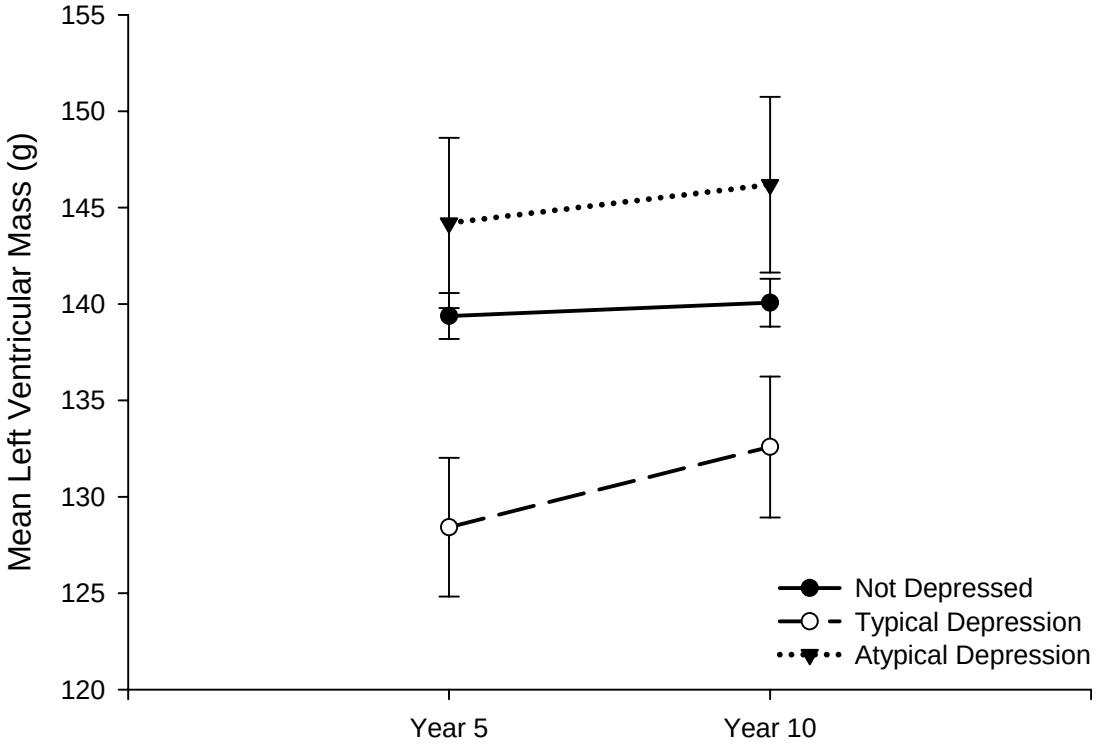
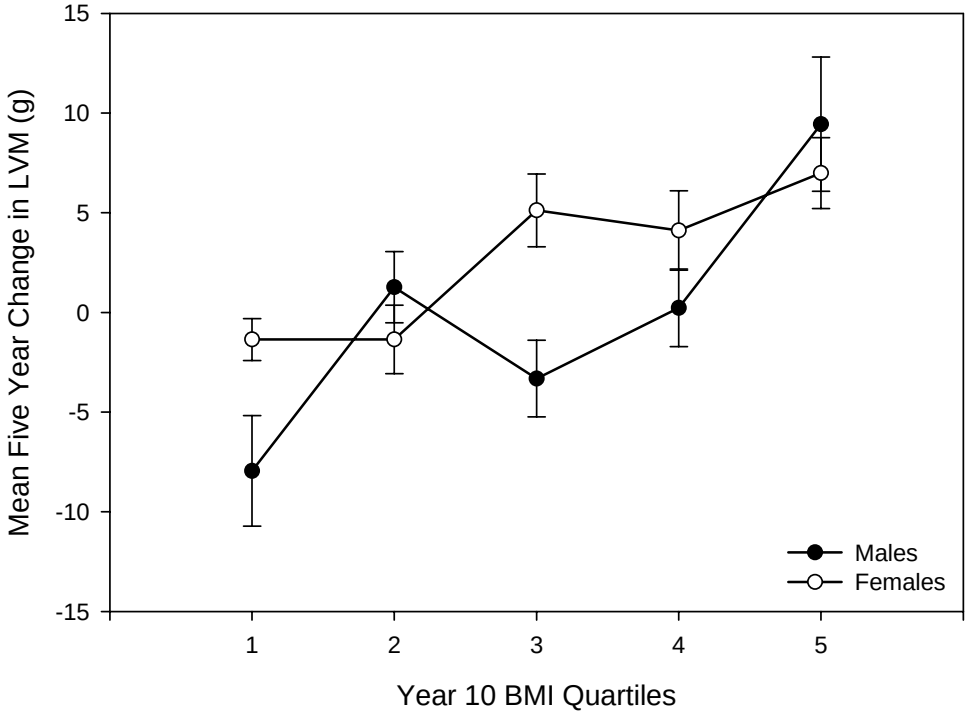


Figure 6: Sex-Specific Change in Left Ventricular Mass Over Time Across BMI and SBP Quartiles (Mean ± SE)



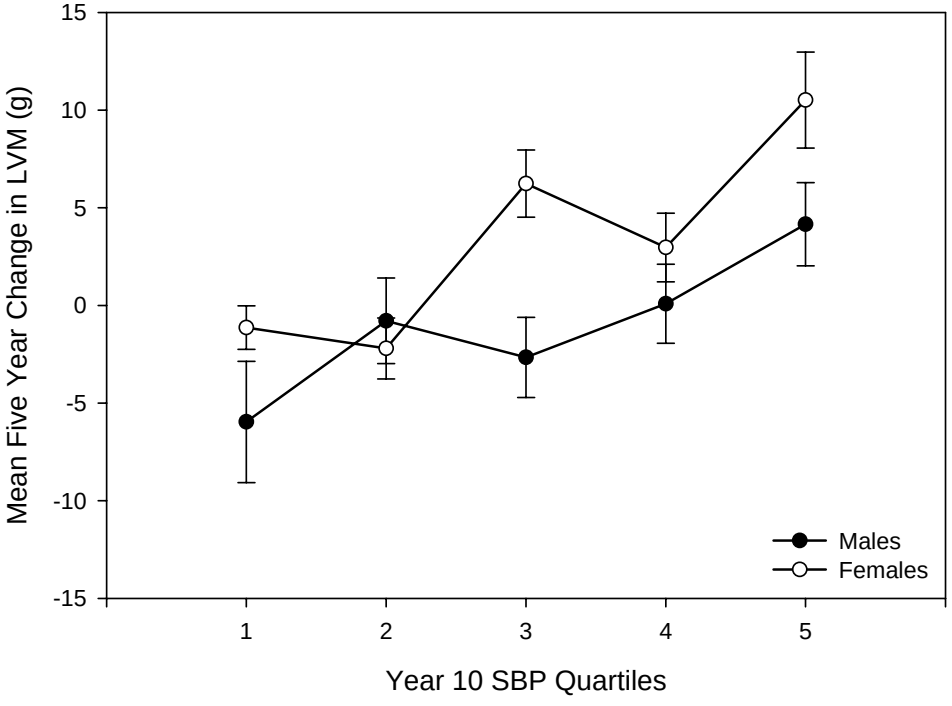
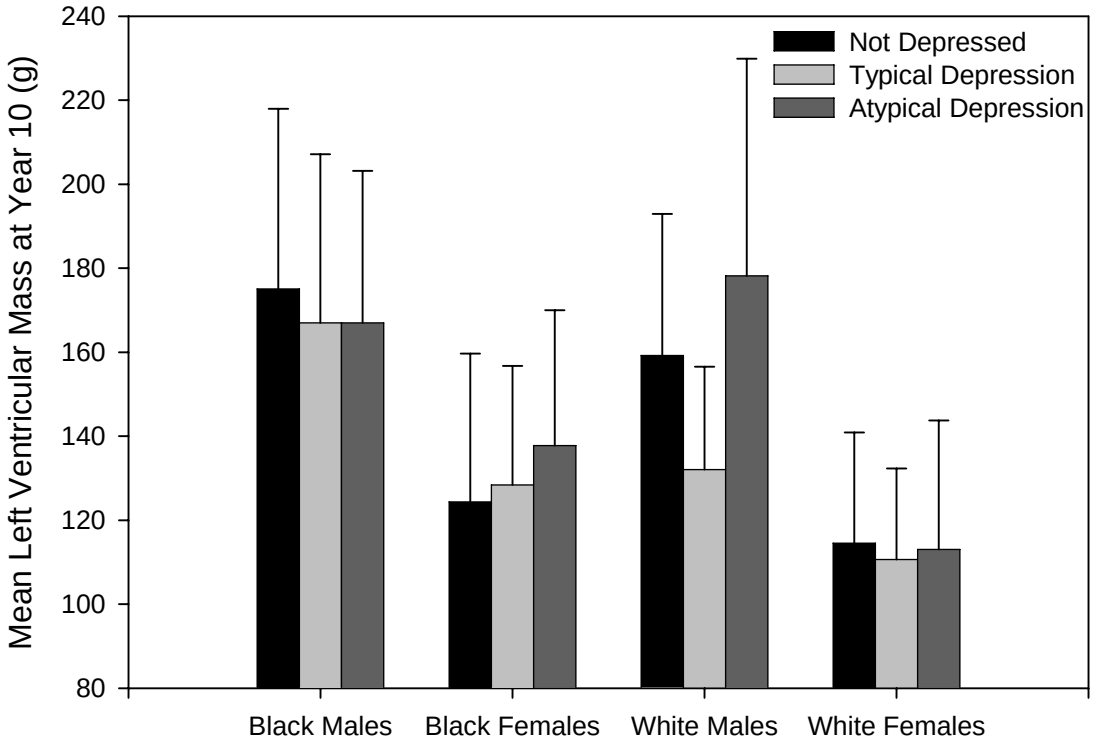


Figure 7: Left Ventricular Mass at Year 10 by sex, race, and depression group (Mean ± SE)



References

Aromaa, A., Raitasalo, R., Reunanen. A., Impivaara, O., Heliovaara, M., Kneckt, P., Lehtinen, V., Joukamaa, M., & Maatela, J. (1994). Depression and cardiovascular diseases. *Acta Psychiatr Scand, 377*, 77-82.

American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders, fourth edition. Washington, DC: American Psychiatric Association.

Angst, J., Gamma, A., Sellaro, R., Zhang, H., & Merikangas, K. (2002). Toward validation of atypical depression in the community: Results of the Zurich cohort study. *Journal of Affective Disorders*, *72(2)*, 125-138.

Baron, R.M., & Kenny, D.A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*, *51(6)*, 1173-82.

Benazzi, F. (1999). Prevalence and clinical features of atypical depression in depressed outpatients: A 467-Case Study. *Psychiatry Research (Ireland)*, *86(3)*, 259-265.

Benazzi, F. (2003). Testing DSM-IV definition of atypical depression. *Ann Clin Psychiatry*, *15(1)*, 9-16.

Blumenthal, J.A., Williams, R.S., Wallace, A.G., Williams, R.B. Jr., Needles, T.L. (1982). Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. Psychosom Med, 44(6), 519-27.

Brook, R.D., & Julius, S. (2000). Autonomic imbalance, hypertension, and cardiovascular risk. *Am J Hypertens*, *13(6 Pt 2)*, 112S-122S.

Brown, C., Schulberg, H.C., & Madonia, M.J. (1996). Clinical presentations of major depression by African Americans and whites in primary medical care practice. *J Affect Disord*, *41(3)*, 181-91.

Brown, E.S., Varghese, F.P., & McEwen, B.S. (2004). Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry*, *55(1)*, 1-9.

Bush, D.E., Ziegelstein, R.C., Tayback, M., Richter, D., Stevens, S., Zahalsky, H., & Fauerbach, J.A. (2001). Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol*, *88(4)*, 337-41.

Camacho, T.C., Roberts, R.E., Lazarus, N.B., Kaplan, G.A., & Cohen, R.D. (1991). Physical activity and depression: evidence from the Alameda County Study. *Am J Epidemiol*, *134(2)*, 220-31.

Carney, R.M., Rich, M.W., Freedland, K.E., & Saini, J. (1988). Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med, 50*, 627-33.

Carney, R.M., Freedland, K.E., Eisen, S.A., Rich, M.W., Jaffe, A.S. (1995). Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol*, *14(1)*, 88-90.

Comstock, G.W., & Helsing, K.J. (1976). Symptoms of depression in two communities. *Psychol Med*, *6*, 551-563.

Cutter, G.R., Burke, G.L., Dyer, A.R., Friedman, G.D., Hilner, J.E., Hughes, G.H., Hulley, S.B., Jacobs, D.R. Jr., Liu, K., Manolio, T.A., et al. (1991). Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials*, *12(1 Suppl)*, 1S-77S.

Dalack, G.W., & Roose, S.P. (1990). Perspectives on the relationship between cardiovascular disease and affective disorder. *J Clin Psychiatry*, *51 Suppl*, 4-11.

Dei Cas, L., Metra, M., Nodari, S., Dei Cas, A., & Gheorghiade, M. (2003). Prevention and management of chronic heart failure in patients at risk. *Am J Cardiol, 91(9A),* 10F-17F.

Dekkers, C., Treiber, F.A., Kapuku, G., Van Den Oord, E.J., & Snieder, H. (2002). Growth of left ventricular mass in African American and European American youth. *Hypertension, 39(5)*, 943-51.

Dunlop, D.D., Song, J., Lyons, J.S., Manheim, L.M., & Chang, R.W. (2003). Racial/ethnic differences in rates of depression among preretirement adults. *Am J Public Health*, *93(11)*, 1945-1952.

East, M.A., Jollis, J.G., Nelson, C.L., Marks, D., & Peterson, E.D. (2003). The influence of left ventricular hypertrophy on survival in patients with coronary artery disease: do race and gender matter? *J Am Coll Cardiol*, *41(6)*, 949-954.

Fergusson, D.M., Goodwin, R.D., & Horwood, L.J. (2003). Major depression and cigarette smoking: Results of a 21-year longitudinal study. *Psychological Medicine*, *33*, 1357–1367.

Ferketich, A.K., Schwartzbaum, J.A., Frid, D.J., & Moeschberger, M.L. (2000). Depression as an antecedent to heart disease among women and men in the NHANES I study. *Arch Intern Med, 160*, 1261-1268.

First, Michael B., Spitzer, Robert L, Gibbon Miriam, and Williams, Janet B.W.: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, D.C.: American Psychiatric Press, Inc., 1996.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1993). Depression following myocardial infarction: impact on 6-month survival. *JAMA, 270*, 1819-1861.

Frasure-Smith, N., Lesperance, F., & Talajic, M. (1995). Depression and 18-month prognosis after myocardial infarction. *Circulation, 91*, 999-1005.

Frasure-Smith, N., & Lesperance, F. (2003). Depression and other psychological risks following myocardial infarction. *Arch Gen Psychiatry*, *60(6)*, 627-36.

Friedman, G.D., Cutter, G.R., Donahue, R.P., Hughes, G.H., Hulley, S.B., Jacobs, D.R. Jr., Liu, K., Savage, P.J. (1988). CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*, *41(11)*, 1105-16.

Gardin, J.M., Savage, D.D., Ware, J.H., & Henry, W.L. (1987). Effect of age, sex, and body surface area on echocardiographic left ventricular wall mass in normal subjects. *Hypertension*, *9(2 Pt 2)*, II36-9.

Gardin, J.M., Wagenknecht, L.E., Anton-Culver, H., Flack, J., Gidding, S., Kurosaki, T., Wong, N.D., & Manolio, T.A. (1995). Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women. The CARDIA study. Coronary Artery Risk Development in Young Adults. *Circulation*, *92(3)*, 380-7.

Gardin, J.M., Brunner, D., Schreiner, P.J., Xie, X., Reid, C.L., Ruth, K., Bild, D.E., & Gidding, S.S. (2002). Demographics and correlates of five-year change in echocardiographic left ventricular mass in young black and white adult men and women: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Am Coll Cardiol*, *40(3)*, 529-35.

Goodman, E., & Capitman, J. (2000). Depressive symptoms and cigarette smoking among teens. *Pediatrics*, *106*, 748–755.

Goodman, E., & Whitaker, R.C. (2002). A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics*, *110*, 497–504.

Gump, B.B., Matthews, K.A., & Raikkonen, K. (1999). Modeling relationships among socioeconomic status, hostility, cardiovascular reactivity, and left ventricular mass in African American and White children. *Health Psychol*, *18(2)*, 140-50.

Harris, P.A. (2004). The impact of age, gender, race, and ethnicity on the diagnosis and treatment of depression. *J Manag Care Pharm*, *10(2 Suppl)*, S2-7.

Iverson, G.L. (2004). Objective assessment of psychomotor retardation in primary care patients with depression. *J Behav Med*, *27(1)*, 31-7.

Iwata, N., Turner, R.J., & Lloyd, D.A. (2002). Race/ethnicity and depressive symptoms in community-dwelling young adults: a differential item functioning analysis. *Psychiatry Res*, *110(3)*, 281-9.

Kahn, J.P., Gorman, J.M., King, D.L., Fyer, A.J., Liebowitz, M.R., & Klein, D.F. (1990). Cardiac left ventricular hypertrophy and chamber dilatation in panic disorder patients: implications for idiopathic dilated cardiomyopathy. *Psychiatry Res*, *32(1)*, 55-61.

Kendler, K.S., Eaves, L.J., Walters, E.E., Neale, M.C., Heath, A.C., & Kessler, R.C. (1996). The identification and validation of distinct depressive syndromes in a population-based sample of female twins. *Arch Gen Psychiatry*, *53(5)*, 391-9.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., & Kendler, K.S. (1994). Lifetime and 12-month prevalence of DSM-

III-R psychiatric disorders in the Unites States: results from the National Comorbidity Survey. *Arch Gen Psychiatry, 51*, 8-19.

Kop, W.J., Gottdiener, J.S., Patterson, S.M., & Krantz, D.S. (2000). Relationship between left ventricular mass and hemodynamic responses to physical and mental stress. *J Psychosom Res, 48*, 79-88.

Lechin, F., van der Dijs, B., Orozco, B., Lechin, M.E., Baez, S., Lechin, A.E., Rada, I., Acosta, E., Arocha, L., Jimenez, V., Leon, G., & Garcia, Z. (1995). Plasma neurotransmitters, blood pressure, and heart rate during supine-resting, orthostasis, and moderate exercise conditions in major depressed patients. *Biol Psychiatry*, *38(3)*, 166-173.

Liao, Y., Cooper, R.S., Mensah, G.A., & McGee, D.L. (1995). Left ventricular hypertrophy has a greater impact on survival in women than in men. *Circulation*, *92(4)*, 805-10.

Lucht, M., Schaub, R.T., Meyer, C., Hapke, U., Rumpf, H.J., Bartels, T., von Houwald, J., Barnow, S., Freyberger, H.J., Dilling, H., & John, U. (2003). Gender differences in unipolar depression: a general population survey of adults between age 18 to 64 of German nationality. *J Affect Disord*, *77(3)*, 203-11.

Luscher, T.F. (1990). Imbalance of endothelium-derived relaxing and contracting factors. A new concept in hypertension? *Am J Hypertens*, *3(4)*, 317-30.

Markovitz, J.H., & Matthews, K.A. (1991). Platelets and coronary heart disease: potential psychophysiologic mechanisms. *Psychosom Med*, *53(6)*, 643-68.

Markovitz, J.H., Raczynski, J.M., Lewis, C.E., Flack, J., Chesney, M., Chettur, V., Hardin, J.M., & Johnson, E. (1996). Lack of independent relationships between left

ventricular mass and cardiovascular reactivity to physical and psychological stress in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Hypertens*, *9(9)*, 915-23.

Mayou, R., Foster, A., & Williamson, B. (1978). Psychosocial adjustment in patients one year after myocardial infarction. *J Psychosom Res*, *22(5)*, 447-53.

Mein, C.A., Caulfield, M.J., Dobson, R.J., & Munroe, P.B. (2004). Genetics of essential hypertension. *Hum Mol Genet*, *13 Spec No 1*, R169-75.

Miyawaki, E., & Salzman, C. (1991). Autonomic nervous system tests in psychiatry: implications and potential uses of heart rate variability. *Integrated Psychiatry*, *7*, 21-28.

Mullins, L.J., Morley, S.D., & Mullins, J.J. (1996). Transgenics and essential hypertension. *J Hum Hypertens*, *10(10)*, 627-31.

Musselman, D.L., Tomer, A., Manatunga, A.K., Knight, B.T., Porter, M.R., Kasey, S., Marzec, U., Harker, L.A., & Nemeroff, C.B. (1996). Exaggerated platelet reactivity in major depression. *Am J Psychiatry*, *153(10)*, 1313-1317.

Musselman, D.L., Evans, D.L., & Nemeroff, C.B. (1998). The relationship of depression to cardiovascular disease. *Arch Gen Psychiatry, 55*, 580-592.

Myers, J.K., & Weissman, M.M. (1980). Use of a self-report symptom scale to detect depression in a community sample. *Am J Psychiatry*, *137(9)*, 1081-4.

Nemeroff, C.B., Widerlov, E., Bissette, G., Walleus, H., Karlsson, I., Eklund, K., Kilts, C.D., Loosen, P.T., & Vale, W. (1984). Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*, *226(4680)*, 1342-1344.

Pine, D.S., Goldstein, R.B., Wolk, S., & Weissman, M.M. (2001). The association between childhood depression and adulthood body mass index. *Pediatrics*, *107*, 1049–56.

Posternak, M.A., & Zimmerman, M. (2001). Symptoms of atypical depression. *Psychiatry Res, 104(2)*, 175-181.

Posternak, M. A., & Zimmerman, M. (2002). Partial validation of the atypical features subtype of major depressive disorder. *Archives of General Psychiatry*, *59(1)*, 70-76.

Pratt, L.A., Ford, D.E., Crum, R.M., Armenian, H.K., Gallo, J.J., & Eaton, W.W. (1996). Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation, 94*, 3123-3129.

Quitkin, F.M. (2002). Depression With Atypical Features: Diagnostic Validity, Prevalence, and Treatment. *Prim Care Companion J Clin Psychiatry*, *4(3)*, 94-99.

Raadsheer, F.C., Hoogendijk, W.J., Stam, F.C., Tilders, F.J., & Swaab, D.F. (1994). Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology*, *60(4)*, 436-444.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Journal of Applied Psychological Measures*, *1(3)*, 385-401.

Roberts, R.E., Strawbridge, W.J., Deleger, S., & Kaplan, G.A. (2002). Are the fat more jolly? *Ann Behav Med*, *24*, 169–80.

Salehian, B., & Kejriwal, K. (1999). Glucocorticoid-induced muscle atrophy: mechanisms and therapeutic strategies. *Endocr Pract*, *5(5)*, 277-81.

Saltos, E., & Bowman, S. (1998). Dietary Guidance on Sodium: Should We Take It With A Grain of Salt? *Family Economics & Nutrition Review, 11(4),* 49-51.

Savage, D.D., Henry, W.L., Mitchell, J.R., Taylor, A.A., Gardin, J.M., Drayer, J.I., & Laragh, J.H. (1979). Echocardiographic comparison of black and white hypertensive subjects. *J Natl Med Assoc*, *71(7)*, 709-12.

Schiffrin, E.L. (2001). A critical review of the role of endothelial factors in the pathogenesis of hypertension. *J Cardiovasc Pharmacol*, *38 Suppl 2*, S3-6.

Schirmer, H., Lunde, P., & Rasmussen, K. (1999). Prevalence of left ventricular hypertrophy in a general population; The Tromso Study. *Eur Heart J*, *20 (6)*, 429-438.

Schnall, P.L., Pieper, C., Schwartz, J.E., Karasek, R.A., Schlussel, Y., Devereux, R.B., Ganau, A., Alderman, M., Warren, K., & Pickering, T.G. (1990). The relationship between "job strain," workplace diastolic blood pressure, and left ventricular mass index. Results of a case-control study. *JAMA*, *263(14)*, 1929-35. Erratum in: *JAMA*, *267(9)*, 1209.

Schneider, G., Kruse, A., Nehen, H.G., Senf, W., & Heuft, G. (2000). The prevalence and differential diagnosis of subclinical depressive syndromes in inpatients 60 years and older. *Psychother Psychosom*, *69(5)*, 251-60.

Schneiderman, N., Saab, P.G., Catellier, D.J., Powell, L.H., DeBusk, R.F., Williams, R.B., Carney, R.M., Raczynski, J.M., Cowan, M.J., Berkman, L.F., Kaufmann, P.G.; ENRICHD Investigators (2004). Psychosocial treatment within sex by ethnicity subgroups in the Enhancing Recovery in Coronary Heart Disease clinical trial. *Psychosom Med*, *66(4)*, 475-83.

Sharp, A., & Mayet, J. (2002). Regression of left ventricular hypertrophy: hoping for a longer life. *J Renin Angiotensin Aldosterone Syst, 3(3),* 141-144.

Shub, C., Klein, A.L., Zachariah, P.K., Bailey, K.R., & Tajik, A.J. (1994). Determination of left ventricular mass by echocardiography in a normal population: effect of age and sex in addition to body size. *Mayo Clin Proc*, *69(3)*, 205-11.

Stern, M.J., Pascale, L., & Ackerman, A. (1977). Life adjustment postmyocardial infarction: determining predictive variables. *Arch Intern Med*, *137(12)*, 1680-5.

Sun, Z.J., & Zhang, Z.E. (2005). Historic perspectives and recent advances in major animal models of hypertension. *Acta Pharmacol Sin*, *26(3)*, 295-301.

Taylor, T.R., Kamarck, T.W., & Dianzumba, S. (2003). Cardiovascular reactivity and left ventricular mass: an integrative review. *Ann Behav Med*, *26(3)*, 182-93.

Troxler, R.G., Sprague, E.A., Albanese, R.A., Fuchs, R., & Thompson, A.J. (1977). The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis*, *26(2)*, 151-162.

Urbina, E.M., Gidding, S.S., Bao, W., Pickoff, A.S., Berdusis, K., & Berenson, G.S. (1995). Effect of body size, ponderosity, and blood pressure on left ventricular growth in children and young adults in the Bogalusa Heart Study. *Circulation, 91(9)*, 2400-2406.

Vakili, B.A., Okin, P.M., & Devereux, R.B. (2001). Prognostic implications of left ventricular hypertrophy. *Am Heart J*, *141(3)*, 334-41.

Weissman, M.M., Sholomskas, D., Pottenger, M., Prusoff, B.A., Locke, B.Z. (1977). Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol*, *106(3)*, 203-14.

Wu, L., & Anthony, J.C. (1999). Tobacco smoking and depressed mood in late childhood and early adolescence. *American Journal of Public Health*, *89*, 1837–1840.

Wulsin, L.R., & Singal, B.M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med*, *65(2)*, 201-10.

Zhang, A.Y., & Snowden, L.R. (1999). Ethnic characteristics of mental disorders in five U.S. communities. *Cultur Divers Ethnic Minor Psychol*, *5(2)*, 134-46.